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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 309/04, 335/02, A61K 31/35 — A1

(11) International Publication Number: **WO 97/29101**

(43) International Publication Date: 14 August 1997 (14.08.97)

(21) International Application Number: PCT/US97/00255

(22) International Filing Date: 2 January 1997 (02.01.97)

(30) Priority Data:
60/011,278 7 February 1996 (07.02.96) US

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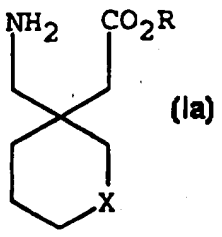
(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KE, KR, LC, LK, LR, LS, LT, LV, MG, MK, MN, MW, MX, NO, NZ, PL, RO, SD, SG, SI, SK, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

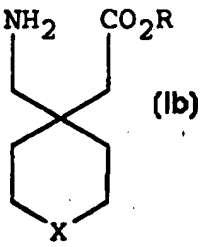
(54) Title: NOVEL CYCLIC AMINO ACIDS AS PHARMACEUTICAL AGENTS

(57) Abstract

Novel cyclic amino acids of formula (Ia) or (Ib) are disclosed and are useful as agents in the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, and neuropathological disorders. Processes for the preparation and intermediates useful in the preparation are also disclosed.



(Ia)



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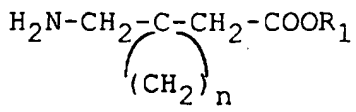
NOVEL CYCLIC AMINO ACIDS AS PHARMACEUTICAL AGENTS

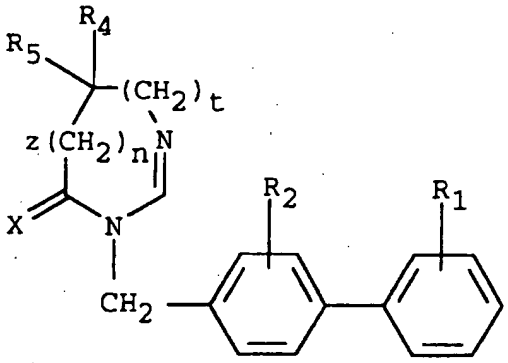
BACKGROUND OF THE INVENTION

Compounds of formula



wherein R_1 is hydrogen or a lower alkyl radical and n is 4, 5, or 6 are known in United States Patent Number 4,024,175 and its divisional United States Patent Number 4,087,544. The uses disclosed are: protective effect against cramp induced by thiosemicarbazide; protective action against cardiazole cramp; the cerebral diseases, epilepsy, faintness attacks, hypokinesia, and cranial traumas; and improvement in cerebral functions. The compounds are useful in geriatric patients. The patents are hereby incorporated by reference.

United States Patent Number 5,270,317 and its divisional United States Patent Number 5,352,788 disclose compounds of formula



in which:

R_1 and R_2 are similar or different and are each independently hydrogen or a group selected from a C_1-C_6 alkyl, a C_1-C_4 alkoxy, an amino, an aminomethyl, a carboxyl, an alkoxycarbonyl in which the alkoxy is C_1-C_4, a cyano, a tetrazolyl, a methyltetrazolyl, a methylsulfonylamino, a trifluoromethylsulfonylamino, a trifluoromethylsulfonylaminomethyl, an N-cyanoacetamide, an N-hydroxyacetamide, an N-(4-carboxy-1,3-thiazol-2-yl)acetamide, a ureido, a 2-cyanoguanidinocarbonyl, a 2-cyanoguanidinomethyl, an imidazol-1-yl-carbonyl, and a 3-cyano-2-methylisothioureidomethyl, with the proviso that at least one of the substituents R_1 or R_2 is other than hydrogen;

R_3 is a hydrogen, a C_1-C_6 alkyl which is unsubstituted or substituted by one or more halogen atoms, a C_2-C_6 alkenyl, a C_3-C_7 cycloalkyl, a phenyl, a phenylalkyl in which the alkyl is C_1-C_3, or a phenylalkenyl in which the alkenyl is C_2-C_3, said phenyl groups being unsubstituted, or monosubstituted or polysubstituted by a halogen atom, a C_1-C_4 alkyl, a C_1-C_4 halogenoalkyl, a C_1-C_4 polyhalogenoalkyl, a hydroxyl, or a C_1-C_4 alkoxy; and either

R_4 and R_5 are each independently a C_1-C_6 alkyl, a phenyl or a phenylalkyl in which the alkyl is C_1-C_3, said alkyl, phenyl, and phenylalkyl groups being unsubstituted or substituted by one or more halogen atoms or by a group selected from a C_1-C_4 perfluoroalkyl, a hydroxyl, and a C_1-C_4 alkoxy;

or R_4 and R_5 together form a group of the formula $=CR_7R_8$, in which R_7 is hydrogen, a C_1-C_4 alkyl or a phenyl, and R_8 is a C_1-C_4 alkyl or a phenyl;

or else R_4 and R_5 together are either a group of the formula $(CH_2)_n$ or a group of the formula $(CH_2)_pY$-$(CH_2)_q$, in which Y is either an oxygen

atom, or a sulfur atom, or a carbon atom substituted by a C_1-C_4 alkyl group, a phenyl or a phenylalkyl in which the alkyl is C_1-C_3, or a group N-R_6, in which R_6 is a hydrogen, a C_1-C_4 alkyl, a phenylalkyl in which the alkyl is C_1-C_3, a C_1-C_4 alkylcarbonyl, a C_1-C_4 alkylcarbonyl, a C_1-C_4 halogenoalkylcarbonyl, a C_1-C_4 polyhalogenoalkylcarbonyl, a benzoyl, an alphaaminoacyl or an N-protecting group, or R_4 and R_5, together with the carbon atom to which they are bonded, form an indane or an adamantane;

p + q = m;

n is an integer between 2 and 11; and

m is an integer between 2 and 5; or

R_4 is a C_1-C_6 alkyl which is unsubstituted or substituted by one or more halogen atoms; and

R_5 is a cycloalkyl or a cycloalkylmethyl, said cycloalkyl being C_3-C_7, which is unsubstituted or substituted by one or more halogen atoms:

or R_4 and R_5 are each a cyclopropyl;

X is an oxygen atom or sulfur atom; and

z and t are zero or one is zero and the other is one; and their salts.

The compounds are disclosed as having the ability to antagonize angiotension II.

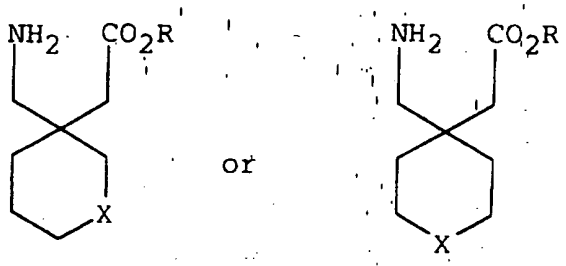
J. Med. Chem., 38:3772-3779 (1995) covers the syntheses of spiropiperidines as potent and selective non-peptide tackykinin NK_2 receptor antagonists.

SUMMARY

The novel cyclic amino acids, their derivatives and pharmaceutically acceptable salts are useful in a variety of disorders. The disorders include: epilepsy, faintness attacks, hypokinesia, cranial

disorders, neurodegenerative disorders, depression, anxiety, panic, pain, and neuropathological disorders.

The compounds are those of formula



I

or a pharmaceutically acceptable salt thereof wherein:

X is O, S, S(O), $S(O)_2$, or NR_1 wherein R_1 is hydrogen, straight or branched alkyl of from 1 to 6 carbon atoms, or benzyl, $-C(O)R_2$ wherein R_2 is straight or branched alkyl of from 1 to 6 carbon atoms, benzyl, or phenyl, $-CO_2R_3$ wherein R_3 is straight or branched alkyl of from 1 to 6 carbon atoms, or benzyl wherein the benzyl and phenyl groups can be unsubstituted or substituted by from 1 to 3 substituents each independently selected from halogen, CF_3, and nitro; and

R is hydrogen or lower alkyl.

Especially preferred compounds of the invention is (4-Aminomethyl-tetrahydro-pyran-4-yl)-acetic acid and (4-Aminomethyl-tetrahydro-thiopyran-4-yl)-acetic acid.

Novel intermediates useful in the preparation of the final products are disclosed as well as a novel process for the preparation of the compounds.

DETAILED DESCRIPTION

The compounds of the instant invention and their pharmaceutically acceptable salts are as defined by Formula I.

The term "alkyl" is a straight or branched group of from 1 to 6 carbon atoms including but not limited to methyl, ethyl, propyl, n-propyl, isopropyl, butyl, 2-butyl, tert-butyl, pentyl, hexyl, and n-hexyl.

Lower alkyl is from 1 to 4 carbon atoms including but not limited to methyl, ethyl, propyl, n-propyl, isopropyl, butyl, n-butyl, isobutyl, and tertbutyl.

The benzyl and phenyl groups may be unsubstituted or substituted by from 1 to 3 substituents selected from halogen, CF_3, and nitro.

Since amino acids are amphoteric, pharmacologically compatible salts when R is hydrogen can be salts of appropriate inorganic or organic acids, for example, hydrochloric, sulphuric, phosphoric, acetic, oxalic, lactic, citric, malic, salicylic, malonic, maleic, succinic, and ascorbic. Starting from corresponding hydroxides or carbonates, salts with alkali metals or alkaline earit metals, for example, sodium, potassium, magnesium, or calcium are formed. Salts with quaternary ammonium ions can also be prepared with, for example, the tetramethyl-ammonium ion. The carboxyl group of the amino acids can be esterified by known means.

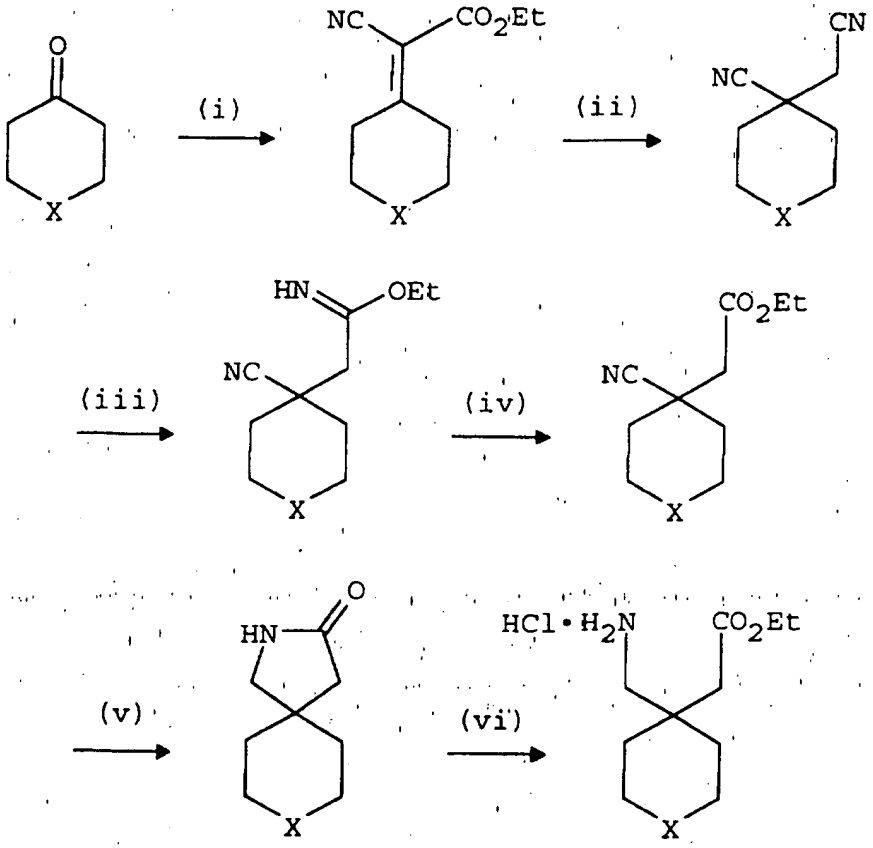
Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R(D) or S(L) configuration. The present invention includes all enantiomeric and epimeric forms as well as the appropriate mixtures thereof.

The compounds of the invention may be synthesized, for example, by utilizing the general strategy

(Scheme 1 below) outlined by Griffiths G., et al., Helv. Chim. Acta, 74:309 (1991). Alternatively, they may also be made as shown (in Scheme 2 below), analogously to the published procedure for the synthesis of 3-oxo-2,8-diazaspiro[4,5]decane-8-carboxylic acid tert-butyl ester (1) (Smith P.W., et al., J. Med. Chem., 38:3772 (1995)). The compounds may also be synthesized by the methods outlined by Satzinger G., et al., (US 4,024,175, and US 4,152,326) (Schemes 3 and 4 below). In the case where X is NR_1 and R is $C(O)R_1$ or CO_2R_3, except where R_3 is a benzyl group, the compounds may be synthesized by the route outlined by Griffiths G., et al., Helv. Chim. Acta, 74:309 (1991) (Scheme 5 below). The compounds may also be synthesised by the method outlined in Scheme 6 below.

Scheme 1



(i) Ethyl cyanoacetate, piperidine (Cope, et al., J. Am. Chem. Soc., 63:3452 (1941))

(ii) NaCN, EtOH/H_2O,

(iii) EtOH, HCl,

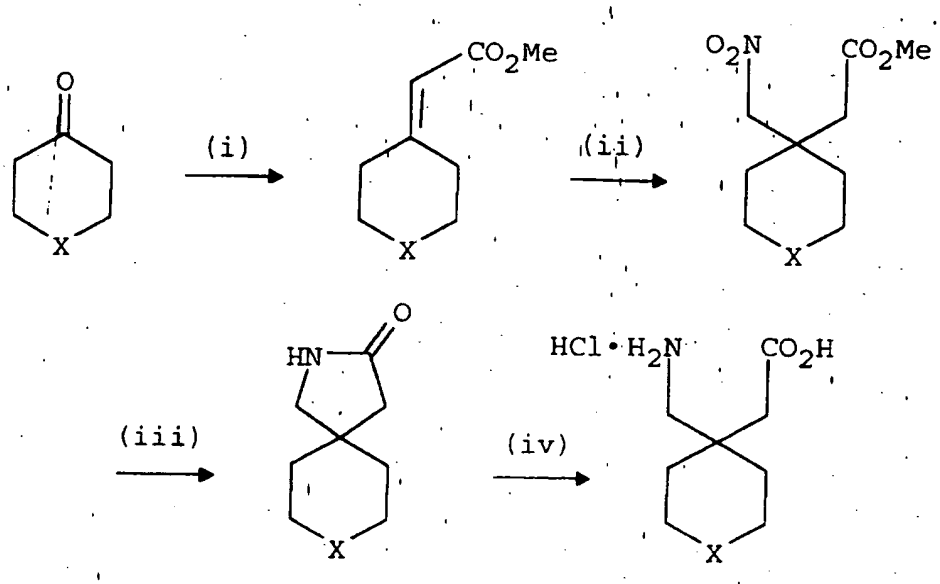
(iv) H_2O/H^+,

(v) H_2, Rh/C, MeOH,

(vi) HCl

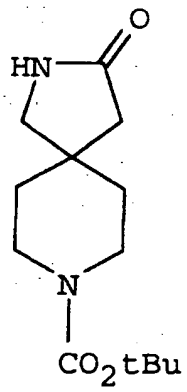
The X moiety can also be in the 3-position.

Scheme 2



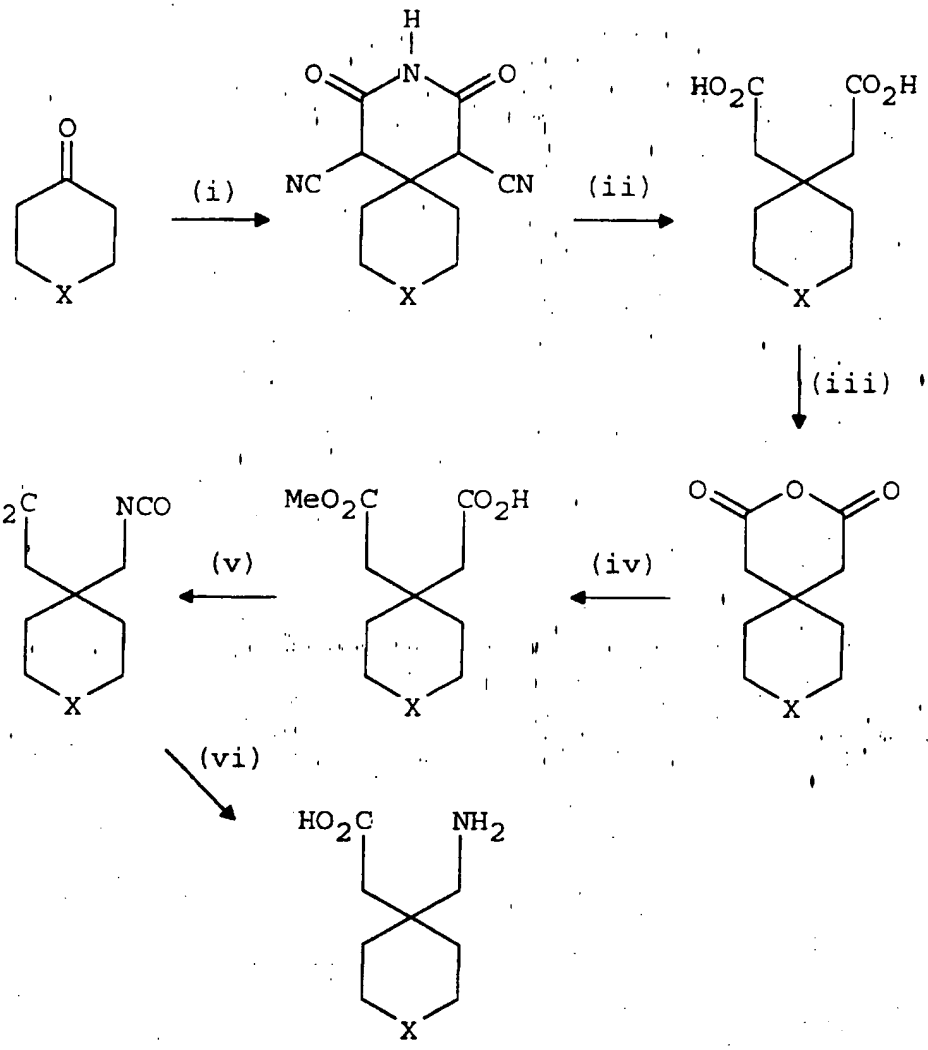
(i) $Ph_3P = CHCO_2Me$,
(ii) $MeNO_2$, 1,1,3,3-tetramethylguanidine,
(iii) Raney nickel, $EtOH/H_2O$,
(iv) HCl

The X moiety can also be in the 3-position.



(1)

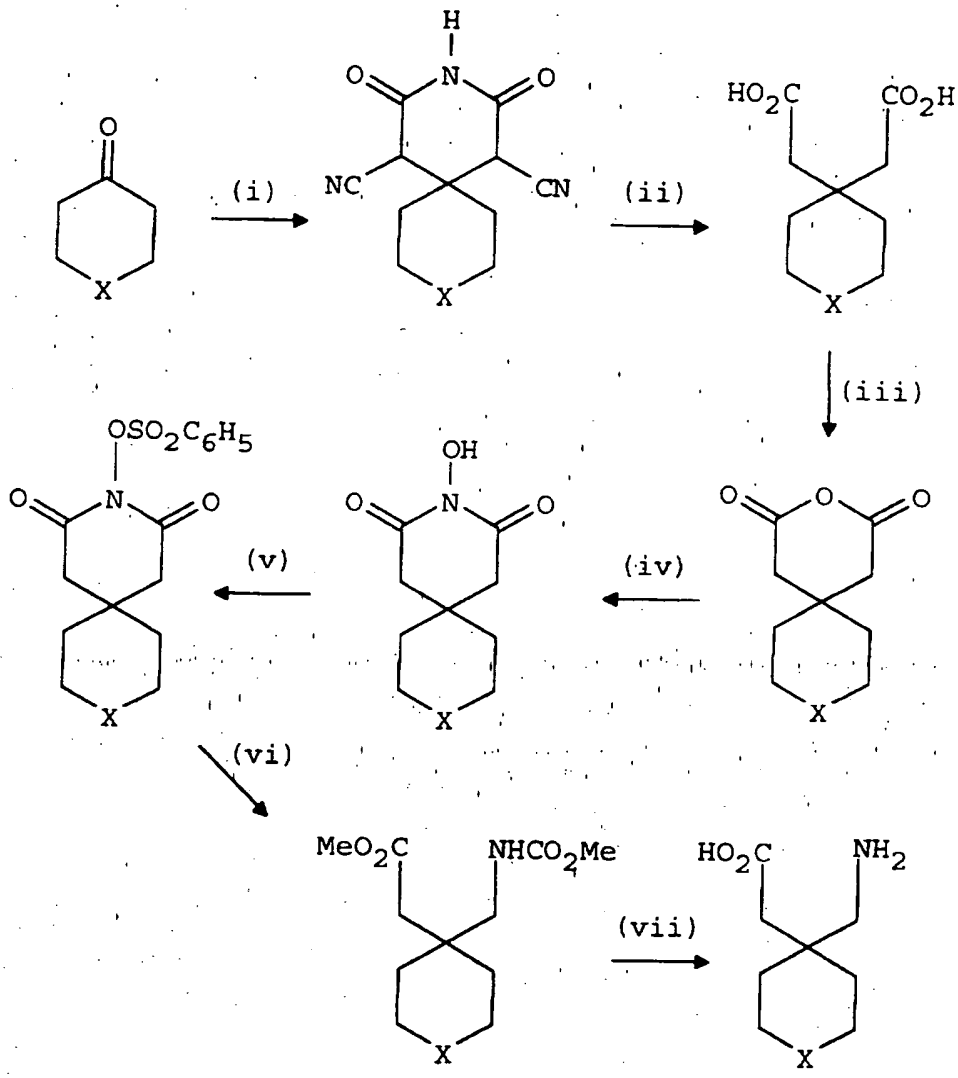
Scheme 3



(i) Ethylcyanoacetate, ammonia then H_3O^+;
(ii) H_2SO_4;
(iii) Ac_2O;
(iv) MeOH;
(v) Curtius Reaction;
(vi) HCl, H_2O then anion exchange

The X moiety can also be in the 3-position.

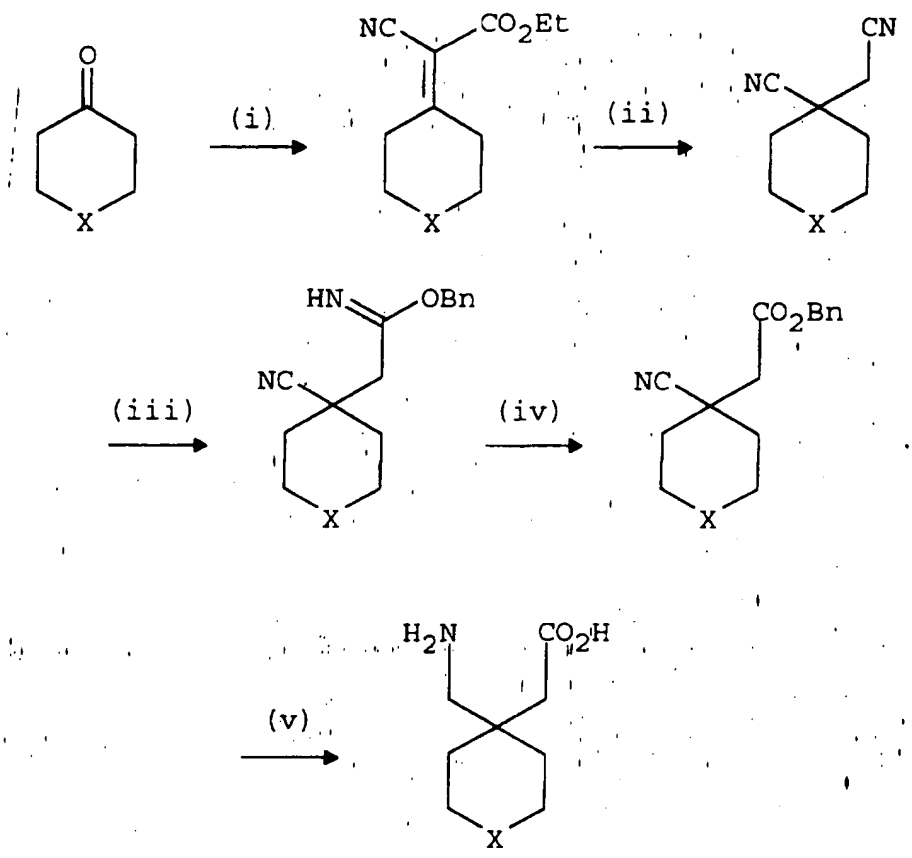
Scheme 4



(i) Ethylcyanoacetate, ammonia then H_3O^+;
(ii) H_2SO_4;
(iii) Ac_2O;
(iv) H_2NOH;
(v) $PhSO_2Cl$;
(vi) Et_3N, MeOH;
(vii) HCl, H_2O then anion exchange

The X moiety can also be in the 3-position.

Scheme 5



(i) Ethyl cyanoacetate, piperidine (Cope, et al., J. Am. Chem. Soc., 63:3452 (1941));

(ii) NaCN, EtOH/H_2O;

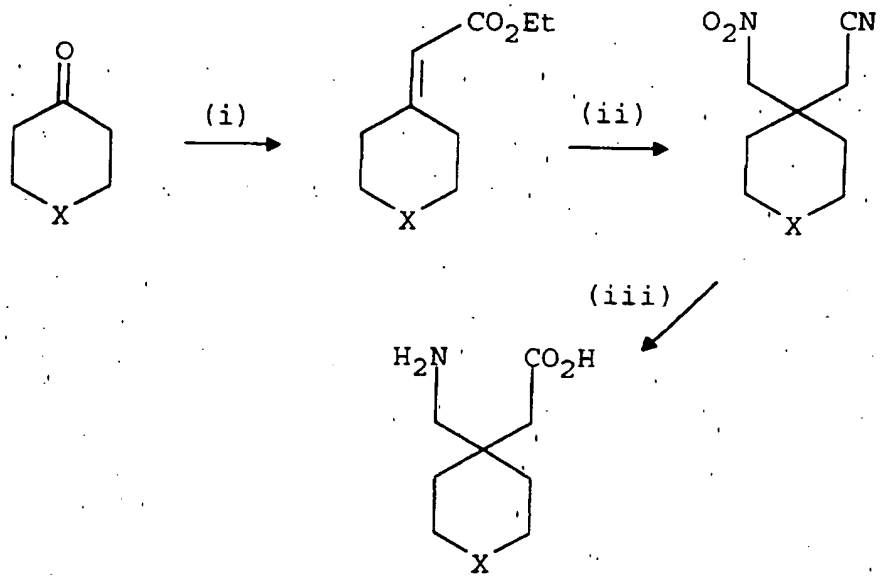
(iii) BnOH, HCl;

(iv) H_2O/H^+;

(v) H_2, Rh/C, MeOH

The X moiety can also be in the 3-position.

Scheme 6



(i) $Ph_3P=CHCO_2Et$,

(ii) $MeNO_2$, tetramethylgaunidine,

(iii) $SnCl_2$, HCl/H_2O

The X moiety can also be in the 3-position.

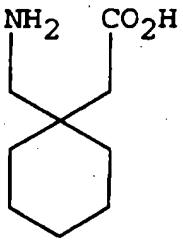
The radioligand binding assay using [^{3}H]gabapentin and the $\alpha_2\delta$ subunit derived from porcine brain tissue was used ("The Novel Anti-convulsant Drug, Gabapentin, Binds to the $\alpha_2\delta$ Subunit of a Calcium Channel", Gee N., et al., J. Biological Chemistry, in press).

TABLE 1

Example No.	IC_{50} (μM)	Number
1	2.75	3
2	0.39	3

Table 1 above shows the binding affinity of Example 1 to the $\alpha_2\delta$ subunit. Gabapentin (Neurontin®) is about 0.10 to 0.12 μM in this assay. The compounds of the instant invention are expected, therefore, to exhibit pharmacologic properties comparable to gabapentin. For example, as agents for convulsions, anxiety, and pain.

The compounds of the invention are related to Neurontin®, a marketed drug effective in the treatment of epilepsy. Neurontin® is 1-(aminomethyl)-cyclohexaneacetic acid of structural formula



The compounds of the invention are also expected to be useful in the treatment of epilepsy. See Table 1 above for IC_{50} data as compared to Neurontin®.

The present invention also relates to therapeutic use of the compounds of the mimetic as agents for neurodegenerative disorders.

Such neurodegenerative disorders are, for example, Alzheimer's disease, Huntington's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis.

The present invention also covers treating neurodegenerative disorders termed acute brain injury. These include but are not limited to: stroke, head trauma, and asphyxia.

Stroke refers to a cerebral vascular disease and may also be referred to as a cerebral vascular incident (CVA) and includes acute thromboembolic stroke. Stroke includes both focal and global ischemia. Also, included are transient cerebral ischemic attacks and other cerebral vascular problems accompanied by cerebral ischemia. A patient undergoing carotid endarterectomy specifically or other cerebrovascular or vascular surgical procedures in general, or diagnostic vascular procedures including cerebral angiography and the like.

Other incidents are head trauma, spinal cord trauma, or injury from general anoxia, hypoxia, hypoglycemia, hypotension as well as similar injuries seen during procedures from embole, hyperfusion, and hypoxia.

The instant invention would be useful in a range of incidents, for example, during cardiac bypass surgery, in incidents of intracranial hemorrhage, in perinatal asphyxia, in cardiac arrest, and status epilepticus.

A skilled physician will be able to determine the appropriate situation in which subjects are susceptible to or at risk of, for example, stroke as well as suffering from stroke for administration by methods of the present invention.

The compounds of the invention are also expected to be useful in the treatment of depression. Depression can be the result of organic disease, secondary to stress associated with personal loss, or idiopathic in origin. There is a strong tendency for familial occurrence of some forms of depression suggesting a mechanistic cause for at least some forms of depression. The diagnosis of depression is made primarily by quantification of alterations in patients' mood. These evaluations of mood are generally performed by a physician or quantified by a neuropsychologist using validated rating scales, such as the Hamilton Depression Rating Scale or the Brief Psychiatric Rating Scale. Numerous other scales have been developed to quantify and measure the degree of mood alterations in patients with depression, such as insomnia, difficulty with concentration, lack of energy, feelings of worthlessness, and guilt. The standards for diagnosis of depression as well as all psychiatric diagnoses are collected in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) referred to as the DSM-IV-R manual published by the American Psychiatric Association, 1994.

GABA is an inhibitory neurotransmitter with the central nervous system. Within the general context of inhibition, it seems likely that GABA-mimetics might decrease or inhibit cerebral function and might therefore slow function and decrease mood leading to depression.

The compounds of the instant invention may produce an anticonvulsant effect through the increase of newly created GABA at the synaptic junction. If gabapentin does indeed increase GABA levels or the effectiveness of GABA at the synaptic junction, then it could be classified as a GABA-mimetic and might decrease or inhibit cerebral function and might,

therefore, slow function and decrease mood leading to depression.

The fact that a GABA agonist or GABA-mimetic might work just the opposite way by increasing mood and thus, be an antidepressant, is a new concept, different from the prevailing opinion of GABA activity heretofore.

The compounds of the instant invention are also expected to be useful in the treatment of anxiety and of panic as demonstrated by means of standard pharmacological procedures.

MATERIAL AND METHODS

Animals

Male Hooded Lister rats (200-250 g) are obtained from Interfauna (Huntingdon, UK) and male TO mice (20-25 g) are obtained from Bantin and Kingman (Hull, UK). Both rodent species are housed in groups of six. Ten Common Marmosets (Callithrix Jacchus) weighing between 280 and 360 g, bred at Manchester University Medical School (Manchester, UK) are housed in pairs. All animals are housed under a 12-hour light/dark cycle (lights on at 07.00 hour) and with food and water ad libitum.

Drug Administration

Drugs are administered either intraperitoneally (IP) or subcutaneously (SC) 40 minutes before the test in a volume of 1 mL/kg for rats and marmosets and 10 mL/kg for mice.

Mouse Light/Dark Box

The apparatus is an open-topped box, 45 cm long, 27 cm wide, and 27 cm high, divided into a small (2/5) and a large (3/5) area by a partition that extended

20 cm above the walls (Costall B., et al., Exploration of mice in a black and white box: validation as a model of anxiety. Pharmacol. Biochem. Behav., 32:777-785 (1989)).

There is a 7.5 x 7.5 cm opening in the center of the partition at floor level. The small compartment is painted black and the large compartment white. The white compartment is illuminated by a 60-W tungsten bulb. The laboratory is illuminated by red light. Each mouse is tested by placing it in the center of the white area and allowing it to explore the novel environment for 5 minutes. The time spent in the illuminated side is measured (Kilfoil T., et al., Effects of anxiolytic and anxiogenic drugs on exploratory activity in a simple model of anxiety in mice. Neuropharmacol., 28:901-905 (1989)).

Rat Elevated X-Maze

A standard elevated X-maze (Handley S.L., et al., Effects of alpha-adrenoceptor agonists and antagonists in a maze-exploration model of 'fear'-motivated behavior. Naunyn-Schiedeberg's Arch. Pharmacol., 327:1-5 (1984)), was automated as previously described (Field, et al., Automation of the rat elevated X-maze test of anxiety. Br. J. Pharmacol., 102(Suppl):304P (1991)). The animals are placed on the center of the X-maze facing one of the open arms. For determining anxiolytic effects the entries and time spent on the end half sections of the open arms is measured during the 5-minute test period (Costall, et al., Use of the elevated plus maze to assess anxiolytic potential in the rat. Br. J. Pharmacol., 96(Suppl):312P (1989)).

Marmoset Human Threat Test

The total number of body postures exhibited by the animal towards the threat stimulus (a human standing approximately 0.5 m away from the marmoset cage and staring into the eyes of the marmoset) is recorded during the 2-minute test period. The body postures scored are slit stares, tail postures, scent marking of the cage/perches, piloerection, retreats, and arching of the back. Each animal is exposed to the threat stimulus twice on the test day before and after drug treatment. The difference between the two scores is analyzed using one-way analysis of variance followed by Dunnett's t-test. All drug treatments are carried out SC at least 2 hours after the first (control) threat. The pretreatment time for each compound is 40 minutes.

Rat Conflict Test

Rats are trained to press levers for food reward in operant chambers. The schedule consists of alternations of four 4-minute unpunished periods on variable interval of 30 seconds signalled by chamber lights on and three 3-minute punished periods on fixed ratio 5 (by footshock concomitant to food delivery) signalled by chamber lights off. The degree of footshock is adjusted for each rat to obtain approximately 80% to 90% suppression of responding in comparison with unpunished responding. Rats receive saline vehicle on training days.

The compounds of the instant invention are also expected to be useful in the treatment of pain and phobic disorders (Am. J. Pain Manag., 5:7-9 (1995)).

The compounds of the instant invention are also expected to be useful in treating the symptoms of manic, acute or chronic, single upside, or recurring.

They are also expected to be useful in treating and/or preventing bipolar disorder (United States Patent Application Number 08/440,570 filed May 15, 1995).

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a compound of Formula I.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium

carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsules, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 1 g according to the particular application and the potency of the active component. In medical use the drug may be administered three times daily as, for example, capsules of 100 or 300 mg. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 0.01 mg to about 100 mg/kg daily. A daily dose range of about 0.01 mg to about 100 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements

of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

The following examples are illustrative of the instant invention; they are not intended to limit the scope.

EXAMPLE 1

(4-Aminomethyl-tetrahydro-pyran-4-yl)-acetic acid

Step 1: Cyanoacetate

A mixture of the ketone (48 mmol), ethyl cyanoacetate (48 mmol), ammonium acetate (4.9 mmol), and glacial acetic acid (9.6 mmol) were refluxed with a Dean Stark trap for 5 hours. The mixture was cooled and washed with H_2O. The H_2O washes were extracted with toluene. The toluene extracts were combined with the original organic layer, dried over $MgSO_4$, and the solvent evaporated to give an orange crystalline solid (8.7 g). Yield 91%. A small sample was recrystallized from ethyl acetate; mp 48-58°C.

^1H NMR ($CDCl_2$) 400 MHz: δ 1.36 (3H, J = 7.0 Hz), 2.80 (2H, t, J = 5.4 Hz), 3.19 (2H, t, J = 5.6 Hz), 3.80 (2H, t, J = 5.4 Hz), 3.87 (2H, t, J = 5.4 Hz), 4.29 (2H, q, J = 5.7 Hz).

MS (CI) m/z: 137, 150, 168, 195, 196 (100% $M+H^+$), 197.

IR (CH_2Cl_2) υ_{max} cm-1: 2988, 2971, 2873, 2229, 1720, 1603, 1467, 1447, 1421, 1390, 1365, 1326, 1278, 1251, 1240, 1211, 1176, 1066, 1034, 1007, 863, 770.

Microanalysis: $C_{10}H_{13}NO_3 \cdot 0.15\ H_2O$:
Calc'd: C, 60.69; H, 6.77; N, 7.08.
Found: C, 60.59; H, 6.62; N, 7.18.

Step 2: Binitrile

To a solution of NaCN (42 mmol) in 6 mL H_2O and 160 mL ethanol (95%) was added the cyanoacetate (42 mmol). After 20 hours at reflux, the cooled solution was filtered, the filtrate acidified with gaseous HCl, and filtered again. The solvent was removed to give an impure orange solid (6.6 g). No further purification was attempted before the next step.

Step 3: Cyanoester

Hydrogen chloride gas was bubbled through an ice-cooled solution of the bis nitrile (2.1 g, 0.014 mol) dissolved in ethanol (100 mL). After standing for 3 days, the mixture was evaporated to dryness.

The residue was dissolved in ice/water and 1N HCl was added to pH 1. The aqueous solution was extracted with ethyl acetate and the extracts dried (over $MgSO_4$), filtered, and evaporated to dryness. Purification by column chromatography eluting with heptane/ethyl acetate 2:1 gave the final compound 0.8 g (30%) which was used without further purification.

Step 4: Lactam

A mixture of the cyanoester (0.8 g, 4.1 mmol), ethanolic ammonia (90 mL) and Raney nickel was shaken under hydrogen overnight. The mixture was filtered and the liquor evaporated to dryness. Trituration with ether gave the product 0.55 g (87%), mp 125-127°C.
^1H NMR ($CDCl_3$) 400 MHz: δ 1.60-1.70 (m, 4H), 2.29 (s, 2H), 3.25 (s, 2H), 3.60-3.75 (m, 4H), 5.85 (bs, 1H).

IR (film) υ_{max} cm^{-1}: 3190, 3100, 2971, 2935, 2852, 1687, 1102.
MS (CI) m/z: 156 (100%) $M+H^+$.
Microanalysis: $C_8H_{13}NO_2$:
Calc'd: C, 61.91; H, 8.44; N, 9.03.
Found: C, 61.57; H, 8.35; N, 8.75.

Step 5: (4-Aminomethyl-tetrahydro-pyran-4-yl)-acetic acid

The lactam (0.45 g, 2.6 mmol) was refluxed in 12N HCl (20 mL) for 24 hours. The aqueous phase was washed with ethyl acetate and then evaporated to dryness. The residue was recrystallized from methanol/ether to give the required product 0.29 g (53%), mp 180-183°C.
^1H NMR (d_6-DMSO) 400 MHz: δ 1.40-1.60 (m, 4H), 2.53 (s, 2H), 3.02 (s, 2H), 3.50-3.70 (m, 4H), 8.02 (s, 3H), 12.45 (bs, 1H).
IR (film) υ_{max} cm^{-1}: 2936, 1712, 1611, 1514, 1398, 1191, 1101, 1026.
MS (ES) m/z: 174 (95%) $M+H^+$.
Microanalysis: $C_8H_{15}NO_3 \cdot HCl \cdot 0.1\ H_2O$:
Calc'd: C, 45.44; H, 7.72; N, 6.62.
Found: C, 45.46; H, 8.07; N, 6.26.

EXAMPLE 2

(4-Aminomethyl-tetrahydro-thiopyran-4-yl)-acetic acid

Step 1: Unsaturated ethyl ester

A solution of tetrahydrothiopyran-4-one (2.5 g, 21.6 mmol) and (carbethoxymethylene) triphenyl-phosphorane (9.0 g, 25.9 mmol) was heated to reflux in toluene for 18 hours. The mixture was cooled and evaporated to dryness. The residue was purified by flash chromatography (silica, ether/hexane 1:1) to give the required product as an oil (3.77 g). Yield 94%.

^{1}H NMR ($CDCl_3$) 400 MHz: δ 1.28 (3H, t, J = 7.2 Hz), 2.50-2.55 (2H, m), 2.74-2.80 (4H, m), 3.18-3.21 (2H, m), 4.15 (2H, q, J = 7.2 Hz), 5.67 (1H, s).
IR (film) υ_{max} cm^{-1}: 1649, 1713, 2908, 2981.
MS (CI) m/z: 187 (15%) $M+H^+$.

Step 2: Nitro ester

The unsaturated ethyl ester (1.0 g, 5.3 mmol) was heated to reflux under nitrogen in nitromethane (50 mL) with tetramethylguanidine (0.5 mL) for 10 hours. After allowing the mixture to cool to room temperature, it was diluted with ethyl acetate and washed with 1N HCl. The organic solution was separated, dried (magnesium sulfate) and the solvent removed in vacuo. The residue was purified by flash chromatography to give a colorless oil (0.41 g).
Yield 31%.
^{1}H NMR ($CDCl_3$) 400 MHz: δ 1.28 (3H, t, J = 7.2 Hz), 1.85-2.00 (4H, m), 2.54 (2H, s), 2.60-2.75 (4H, m), 4.17 (2H, q, J = 7.2 Hz), 4.72 (2H, s).
IR (film) υ_{max} cm^{-1}: 1374, 1458, 1549, 1728.
MS (EI) m/z: 247 (100%) M^1.

Step 3: (4-Aminomethyl-tetrahydro-thiopyran-4-yl)-acetic acid

The nitro ester (0.4 g, 1.62 mmol) was dissolved in concentrated hydrochloric acid with tin (II) chloride (1.5 g). The mixture was heated to 100°C for 2 hours. The mixture was then evaporated to dryness. The residue was purified by reverse phase chromatography to give colorless crystals (0.10 g).
Yield 26%.
^{1}H NMR (d_6-DMSO) 400 MHz: δ 1.65-1.80 (4H, m), 2.44 (2H, s), 2.54-2.67 (4H, m), 2.95 (2H, s), 7.99 (3H, br s), 12.42 (1H, br s).
IR (film) υ_{max} cm^{-1}: 1525, 1582, 1712, 2959, 3382.

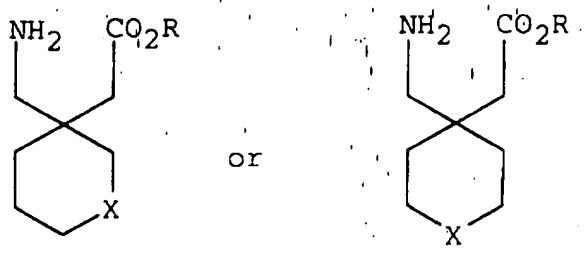
Microanalysis: $C_8H_{15}NO_2S \cdot HCl \cdot 0.75\ H_2O$:

Calc'd: C, 40.16; H, 7.37; N, 5.86.

Found: C, 40.39; H, 7.31; N, 5.98.

CLAIMS

1. A compound of formula



I

or a pharmaceutically acceptable salt thereof wherein:

X is O, S, S(O), $S(O)_2$, or NR_1 wherein R_1 is hydrogen, straight or branched alkyl of from 1 to 6 carbon atoms, benzyl, $-C(O)R_2$ wherein R_2 is straight or branched alkyl of from 1 to 6 carbon atoms, benzyl, or phenyl, or $-CO_2R_3$ wherein R_3 is straight or branched alkyl of from 1 to 6 carbon atoms, or benzyl wherein the benzyl and the phenyl groups can be unsubstituted or substituted by from 1 to 3 substituents each independently selected from halogen, CF_3, and nitro; and

R is hydrogen or lower alkyl.

2. A compound according to Claim 1 wherein X is O.

3. A compound according to Claim 1 wherein X is S.

4. A compound according to Claim 1 wherein X is S(O).

5. A compound according to Claim 1 wherein X is $S(O)_2$.

6. A compound according to Claim 1 wherein X is NR_1, wherein R_1 is hydrogen, straight or branched alkyl

of from 1 to 6 carbon atoms, benzyl, $-C(O)R_2$ wherein R_2 is straight or branched alkyl of from 1 to 6 carbon atoms, benzyl, or phenyl, $-CO_2R_3$ wherein R_3 is straight or branched alkyl of from 1 to 6 carbon atoms, or benzyl.

7. A compound according to Claim 6 wherein X is NH.

8. A compound according to Claim 6 wherein X is NR_1 wherein R_1 is straight or branched alkyl of from 1 to 6 carbon atoms or is benzyl.

9. A compound according to Claim 6 wherein X is NR_1 wherein R_1 is $-C(O)R_2$ wherein R_2 is straight or branched alkyl of from 1 to 6 carbon atoms, benzyl, or phenyl.

10. A compound according to Claim 6 wherein X is $-CO_2R_3$ wherein R_3 is straight or branched alkyl of from 1 to 6 carbon atoms or benzyl.

11. A compound named (4-Aminomethyl-tetrahydro-pyran-4-yl)-acetic acid or (4-Aminomethyl-tetrahydro-thiopyran-4-yl)-acetic acid.

12. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 1 and a pharmaceutically acceptable carrier.

13. A method for treating epilepsy comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

14. A method for treating faintness attacks, hypokinesia, and cranial disorders comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

15. A method for treating neurodegenerative disorders comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

16. A method for treating depression comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

17. A method for treating anxiety comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

18. A method for treating panic comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

19. A method for treating pain comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

20. A method for treating neuropathological disorders comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 97/00255

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D309/04 C07D335/02 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 024 175 A (G.SATZINGER) 17 May 1977 cited in the application see column 1 - column 8	1,12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 March 1997	26.03.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 97/00255

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 13-20 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No
PCT/US 97/00255

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